REMARKS

Applicant respectfully traverses the rejection of the claims of the present invention. The Examiner relies on the Rao et al. patent and the abstract by Kiyosuke et al. and the article by Takaishi et al. to reject the claims of the present invention. As the Examiner recognizes, Rao et al. and Kiyosuke et al. only disclose that cancer may be treated with the compounds disclosed therein. There is no suggestion in either disclosure that Epstein Barr virus may be treated in accordance with the method claim in the present invention. In addition, there is no suggestion that the compositions in Rao et al. or Kiyosuke et al. either inhibits the expression of latent viral antigens of the Epstein Barr associated herpesvirus. The Takaishi et al. article does not suggest that glycyrrhizic acid or glycyrrhetenic acid be used to treat Epstein Barr associated herpesvirus.

The addition of new claims 11, 12, 27 and 28 are patentable over the prior art because they are directed to a method of treating the Epstein Barr virus comprising the steps of administering to the patient a therapeutic amount of glycyrrhizic acid or a derivative of triterpenoid acid so that the glycyrrhizic acid inhibits the transcription or expression of latent viral genes of the Epstein Barr virus associated with herpesvirus. The Kioyuske et al. abstract relied on by the Examiner refers to a glycyrrhetinic acid derivative being helpful to prevent and treatment of diseases related to increases in extracellular matrix formation including liver cirrhosis, interstitial lung disease, chronic renal disease, heart hypertrophy, and cancer metastasis. Nowhere does Kioyuske et al.

suggest that glycyrrhetinic acid has any applicability Epstein Barr virus. Furthermore, there is no indication that Kiyosuke et al. inhibits the transcription of latent genes of the Epstein Barr virus, or inhibits the expression of latent viral antigens of the Epstein Barr virus.

The present invention is not directed to the early antigen activation but the latent cycle of EBV. EBV is a g-herpesvirus, and like all other herpesvirus, EBV can cause an acute infection (lytic cycle) followed by latent infection (latent cycle). During the latent cycle, herpesviruses persist in a non-infectious form with intermittent periods of viral reactivation and shedding. This virus is capable of causing a productive infection in certain cells or under certain conditions and a non-permissive infection in other cells. The important issues are the mechanisms through which the cytopathic potential of the herpesviruses are limited so they can establish latency. During the lytic cycle, viruses infect and kill the cells, but they are cleared by the host immune response and disappear from the host organism. When the viruses are maintained in a latent form they persist over a long term in a host without any cytopathic effect; however, they can reactivate or induce changes in cellular mechanisms, which consequentially, can lead to cellular proliferation and transformation. (See Fields Virology third edition, vol. 2 Chapter 73 and 74 and Fundamental Virology third edition Chapter 7 and 9. Therefore one major goal of treatment of infected individual is to block the viral latent cycle in order to clear the host cells of viral DNA to avoid any consequences related to latency.

The EBV lytic cycle can be activated by treatment with the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) 1. Antiviral drugs currently used

(e.g.etoposide dactinomicin a-interferon, and saponins, foscarnet, cidofovir, gancyclovir etc.) are active against the viral lytic cycle 2-5, but so far, none of them has being shown to be active against the viral latent cycle. Therefore while the drug blocks acute infection, the latent cycle is not affected, the virus is still present in the host cell, and it can eventually reactivate or lead to cellular transformation.

Glycyrrhizic acid is the first compound that inhibits the transcription and the expression of viral latent genes of Epstein Barr virus associated herpesvirus (EBVHV) and as a consequence the viral latent cycle is blocked. Glycyrrhizic acid, therefore, can cause a complete clearance of the virus from the host cells.

Claims 7 and 8 have been rejected as being anticipated by Kiyosuke et al. and Rao et al. Claims 7 and 8 have been canceled, and new claims added which further define the invention. The new claims 11- 28 are directed to a method for treating Epstein Barr virus, which overcomes the Examiner's rejections with regard to claims 7 and 8 directed to the pharmaceutical composition.

Claim 5 has been rejected as obvious over Takaishi et al. in view of Kiyosuke et al.. Takaishi et al. does not teach or suggest the use of glycyrrhizic acid or glycyrrhetinic acid to treat the Epstein Barr associated with herpesvirus. The Examiner relies on Takaishi et al. publication to reject the claims of the present invention. As the Examiner recognizes Takaishi et al. discloses different triterpenoids. There is absolutely no suggestion that Epstein Barr virus (EBV) may be treated in accordance with the method claimed in the present application. In addition, there is no suggestion that the compositions in Takaishi et al. inhibits the transcription of viral latent genes of the EBV

associated with herpesvirus, or inhibits the expression of latent viral antigens of the EBV associated with herpesvirus. Takaishi et al. discusses anti-tumor-promoting activities of dihydroagarofuran sequiterpenes for inhibition of 12-O-tetradecanoylphorbol-13-acetate (TPA) 1 induced Epstein-Barr virus early antigen activation.

Furthermore, although Kiyosuke et al. contemplates the treatment of human cancer cell lines it does not specify what type of cancers cells this is effective against. Heat shock protein (HSP) 47 has been identified as collagen-binding stress protein, shown to have a specific role in the intracellular processing of procollagen molecules during collagen assembly. Increased levels of HSP47 may have correlation to the existence of diseases related to increases in extracellular matrix formation, such as liver cirrhosis, and interstitial fibrosis. Kiyosuke et al. does not disclose any correlation between the glycyrrhetinic acid and Epstein Barr virus and it is not reasonable to use the process of Takaishi et al, in view of Kiyosuke et al., and to use the triterpenoid acid like those disclosed by Kiyosuke to treat Epstein Barr virus.

Epstein Barr virus (EBV) is a member of the herpesvirus family and one of the most common human viruses. In the United States, as many as 95% of adults between 35 and 40 years of age have been infected (Center of Disease Control 2003). EBV establishes a lifelong dormant infection in some cells of the body's immune system. However, the emergence of Burkitt's lymphoma occurs as a late event in very few carriers and is a rare cancer that is not normally found in the United States. EBV is not the sole cause of the disease and therefore any correlation between EBV and cancer is not obvious. To date there is no cure for EBV. More importantly, there exists a multiplicity

of cancers and a unique treatment method for each form of cancer. Importantly, Kioyusuke et al. does not teach treatment of Burkitt's lymphoma.

Furthermore, the Rao et al. patent relied on by the Examiner has a totally different approach. The objects Rao et al. are related to inflammation, cell-cell adhesion and host inflammatory immunoresponse. Rao et al. discloses that

"for certain cancers to successfully spread throughout a person body cell-cell adhesion must take place. This adhesion can be interrupted by the administration of compounds, which generally aid in blocking cell-cell adhesion. Accordingly, compounds of the invention can be used to retard the spread of cancer cells which display receptors which adhere to a compound of formula I." See e.g. Col. 4, line 55-61.

Rao et al. also suggests that a second unexpected property of the compounds disclosed in Rao et al. is that they are inhibitors of enzymes involved in leukotriene biosynthesis. According to Rao et al. leukotrienes are involved in initiating the inflammatory response. Therefore, Rao does not suggest any viral treatment with Glycyrrhizic acid or its inhibition of the viral latent cycle in herpesviruses specifically. As stated above there is no direct association of Epstein Barr Virus with Burkitt's lymphoma to make it obvious to expect to use any triterpenoid to treat Epstein Barr Virus.

Furthermore the new claims 11 – 28 are directed to a method for treating Epstein Barr Virus and in light of the arguments made above are patentable over the prior art cited by the Examiner.

CONCLUSION

For the foregoing reasons the rejection of the claims should be withdrawn and the application be passed to issue.

Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that the foregoing Amendment was mailed by first class mail; postage prepaid, in an envelope addressed to the Hon. Commissioner of Patents and Trademarks, Washington D.C. 20231, this 26th day of January, 2004.

Thomas A. O'Rourke